(FILE 'HOME' ENTERED AT 11:35:14 ON 11 FEB 2003)

FILE 'MEDLINE, BIOTECHDS, EMBASE, CAPLUS, CANCERLIT, BIOSIS' ENTERED AT 11:35:36 ON 11 FEB 2003

L1	5638	S	TP1 OR TP1 OR TERMINAL PROTEIN
L2	451602	S	PROMOTER
L3	508	S	L2 AND L1
L4	50831	S	EBNA# OR EBV
L5	79	S	L4 AND L3
L6	22		DUP REM L5 (57 DUPLICATES REMOVED)

L6 ANSWER 22 OF 22 MEDLINE DUPLICATE 16
AN 90063555 MEDLINE
DN 90063555 PubMed ID: 2555438
TI The **terminal protein** gene 2 of Epstein-Barr virus is transcribed from a bidirectional latent **promoter** region.
AU Laux G; Economou A; Farrell P J
CS Ludwig Institute for Cancer Research, St Mary's Hospital Medical School, London, U.K.
SO JOURNAL OF GENERAL VIROLOGY, (1989 Nov) 70 (Pt 11) 3079-84.
Journal code: 0077340. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199001
ED Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19900103
AB The intact **terminal protein** genes (**TP1** and TP2) of Epstein-Barr virus (**EBV**) are created upon infection by circularization of the linear viral genome at its terminal repeats. The structure of the 1.7 kb TP2 latent mRNA has been determined by cDNA analysis and Northern blotting, revealing its close relation to **TP1** mRNA. The 1.7 kb transcript is expressed from a different **promoter** and has a different 5' exon from **TP1** but is also spliced across the terminal repeats. The last eight exons are common to the **TP1** and TP2 RNAs. The TP2 **promoter** is 3.3 kb downstream of the **TP1 promoter** and is part of a bidirectional latent **EBV promoter** region transcribing the TP2 and the latent membrane protein RNAs in opposite directions.

L6 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2003 ACS
AN 1994:407122 CAPLUS
DN 121:7122
TI the Epstein-Barr virus nuclear antigen 2 (**EBNA2**) transactivates the **terminal protein** 1 gene by interacting with a cis-element located in the **promoter** region
AU Zimber-Strobl, Ursula; Kremmer, E.; Graesser, F.A.; Laux, G.; Bornkamm, G.
CS Inst. Klin. Molekularbiol. Tumorgenet., Muenchen, 8000, Germany
SO Colloque INSERM (1993), 225(Epstein-Barr Virus and Associated Diseases), 159-64
CODEN: CINMDE; ISSN: 0768-3154
DT Journal
LA English
AB **EBNA2** interacts with an enhancer-like cis-element of the **TP1 promoter**. Gel-shift anal. in the presence of in vitro translated **EBNA2** indicates that **EBNA2** interacts indirectly with the cis-element. Cloning of the cellular factors interacting with the **EBNA2** responsive region will further elucidate the mechanism of **EBNA2**-mediated transactivation.

L6 ANSWER 8 OF 22 MEDLINE DUPLICATE 6
AN 95018663 MEDLINE
DN 95018663 PubMed ID: 7933133
TI Crucial sequences within the Epstein-Barr virus **TP1 promoter** for **EBNA2**-mediated transactivation and interaction of **EBNA2** with its responsive element.
AU Meitinger C; Strobl L J; Marschall G; Bornkamm G W; Zimber-Strobl U
CS Institut fur Klinische Molekularbiologie und Tumorgenetik im Forschungszentrum fur Umwelt und Gesundheit, GSF, Munich, Germany.
SO JOURNAL OF VIROLOGY, (1994 Nov) 68 (11) 7497-506.
Journal code: 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199411
ED Entered STN: 19941222
Last Updated on STN: 19941222
Entered Medline: 19941117
AB **EBNA2** is one of the few genes of Epstein-Barr virus which are necessary for immortalization of human primary B lymphocytes. The **EBNA2** protein acts as a transcriptional activator of several viral and cellular genes. For the **TP1 promoter**, we have shown previously that an **EBNA2**-responsive element (EBNA2RE) between -258 and -177 relative to the **TP1** RNA start site is necessary and sufficient for **EBNA2**-mediated transactivation and that it binds **EBNA2** through a cellular factor. To define the critical cis elements within this region, we cloned EBNA2RE mutants in front of the **TP1** minimal **promoter** fused to the reporter gene for luciferase. Transactivation by **EBNA2** was tested by transfection of these mutants in the absence and presence of an **EBNA2** expression vector into the established B-cell line BL41-P3HR-1. The analysis revealed that two identical 11-bp motifs and the region 3' of the second 11-bp motif are essential for transactivation by **EBNA2**. Methylation interference experiments indicated that the same cellular factor in the absence of **EBNA2** binds either one (complex I) or both (complex III) 11-bp motifs with different affinities, giving rise to two different specific protein-DNA complexes within the left-hand 54 bp of EBNA2RE. A third specific complex was shown previously to be present only in **EBNA2**-expressing cells and to contain **EBNA2**. Analysis of this **EBNA2**-containing complex revealed the same protection pattern as for complex III, indicating that **EBNA2** interacts with DNA through binding of the cellular protein to the 11-bp motifs. Mobility shift assays with the different mutants demonstrated that one 11-bp motif is sufficient for binding the cellular factor, whereas for binding of **EBNA2** as well as for efficient transactivation by **EBNA2**, both 11-bp motifs are required.

L6 ANSWER 4 OF 22 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
AN 1995-09664 BIOTECHDS
TI New defective adeno virus containing gene for thymidine-kinase; application in cancer, HIV virus, hepatitis virus, etc. gene therapy
AU Dedieu J F; Le Roux A; Perricaudet M
PA Rhone-Poulenc-Rorer
PI WO 9514102 26 May 1995
AI WO 1994-FR1285 7 Nov 1994
PRAI FR 1993-13772 18 Nov 1993
DT Patent
LA French
OS WPI: 1995-206710 [27]
AB A new defective recombinant adeno virus (AV) contains a DNA sequence (I) encoding thymidine-kinase (TK, EC-2.7.1.21). A preferred virus lacks genomic regions necessary for replication in target cells and is especially based in human AV 5 or dog CAV-2. (I) is derived from human herpes simplex virus and is under control of a viral **promoter**, e.g. E1A, MLP, cytomegalo virus or especially Rous-sarcoma virus. The virus may also include an expression signal sequence specifically active in tumor cells, particularly 1 corresponding to the nuclear antigen **EBNA1**, induced by Epstein-Barr or papilloma viruses. Optionally, the expression sequence is a chimeric **promoter** consisting of **EBNA1** fused upstream to another viral **promoter** particularly that of the **terminal protein**-1 (**TP1**) gene. The new virus may be produced recombinantly in 293 cells. This virus is used in gene therapy to prevent and/or treat cancers, specifically nasopharyngeal cancer, brain tumors and liver cancers. In the presence of a therapeutic agent (e.g. ganciclovir) the virus causes selective destruction of cancer cells and cells infected by e.g. HIV virus or hepatitis virus. (24pp)

(FILE 'MEDLINE, CANCERLIT, BIOTECHDS' ENTERED AT 11:11:06 ON 11 FEB 2003)
DEL HIS

L1	8	S	BCR2 PROMOTER
L2	5		DUP REM L1 (3 DUPLICATES REMOVED)
L3	4050	S	EBNA#
L4	38661	S	ADENOVIR?
L5	49	S	L3 AND L4
L6	27		DUP REM L5 (22 DUPLICATES REMOVED)
L7	117	S	E1A PROMOTER
L8	0	S	L7 AND L3
L9	5	S	MAJOR LATER PROMOTER AND ADENOVIR?
L10	148	S	MLP AND ADENOVIR?
L11	153	S	L10 OR L9
L12	0	S	L11 AND L3

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, CANCERLIT, BIOTECHDS' ENTERED AT 11:28:31 ON 11 FEB 2003

L13	0	S	L12
L14	0	S	L8
L15	154	S	L5
L16	74		DUP REM L15 (80 DUPLICATES REMOVED)

=>

L2 ANSWER 1 OF 5 MEDLINE DUPLICATE 1
AN 1998290296 MEDLINE
DN 98290296 PubMed ID: 9628332
TI Analysis of methylation patterns in the regulatory region of the latent Epstein-Barr virus promoter BCR2 by automated fluorescent genomic sequencing.
AU Takacs M; Myohanen S; Altiok E; Minarovits J
CS Department of Virology, National Institute of Hygiene, Budapest, Hungary.
SO BIOLOGICAL CHEMISTRY, (1998 Apr-May) 379 (4-5) 417-22.
Journal code: 9700112. ISSN: 1431-6730.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AJ000877; GENBANK-AJ000878
EM 199808
ED Entered STN: 19980820
Last Updated on STN: 19980820
Entered Medline: 19980811
AB We analyzed the methylation patterns of CpG dinucleotides in the regulatory region of the latent Epstein-Barrvirus (EBV) promoter BCR2 (also called C promoter, Cp) using automated fluorescent genomic sequencing after bisulfite-induced modification of DNA. BCR2 is one of the alternative promoters for transcripts encoding the growth-transformation-associated nuclear antigens EBNA 1-6 which are expressed in a host cell phenotype dependent manner. Well characterized clones isolated from the Burkitt's lymphoma (BL) line Mutu differing from each other as to their phenotype and EBV latent gene expression were used in the present study. We found that in Mutu BL III clone 99 which is actively using the **BCR2 promoter** the regulatory sequences are unmethylated with two exceptions (position 10702 and 10799). In contrast, there are 15 methylated cytosines in the same region in Mutu BL I clone 216 where the **BCR2 promoter** is silent. Cytosines which are potential targets of DNA methyltransferase in the immediate vicinity or within the attachment sites of cellular C promoter binding factors CBF1 and CBF2 remained hypomethylated in Mutu BL I clone 216. This suggests a role for a hypermethylated region (nucleotides 10666 -10865, -639 to -440 bases upstream from the beginning of the TATA box at position 11305) in silencing of the **BCR2 promoter** in these cells.

L6 ANSWER 23 OF 27 MEDLINE DUPLICATE 20
AN 89007217 MEDLINE
DN 89007217 PubMed ID: 2844682
TI Expression of the Epstein-Barr virus encoded **EBNA**-1 gene in stably transfected human and murine cell lines.
AU Patel G V; Masucci M G; Winberg G; Klein G
CS Department of Tumor Biology, Karolinska Institutet, Stockholm, Sweden.
SO INTERNATIONAL JOURNAL OF CANCER, (1988 Oct 15) 42 (4) 592-8.
Journal code: 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198811
ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881121
AB Five murine and 3 human tumor cell lines were transfected with a retroviral vector that carries the EBV encoded **EBNA**-1 gene. All cell lines expressed intranuclear **EBNA**-1 as detected by anticomplement immunofluorescence and Western blot assays. The cell lines differed in the level of **EBNA**-1 expression and the size of the protein. The internal major late promoter of **adenovirus** was efficient in directing the transcription of **EBNA**-1 in the human lymphoma line BJAB, the murine T-cell lymphoma Tikaut, RBL-5, EL-4 and in the mouse sarcoma line MSWBS but was less efficient in Ramos, an EBV negative Burkitt lymphoma line, the human T-cell leukemia line 1301TK and the P815-X2 mouse mastocytoma line. All transfected lines except MSWBS contained **EBNA**-1 in a truncated form. The truncated **EBNA** -1 polypeptide reacted with the conventional human antibody reagents in an **EBNA** specific fashion but failed to bind rabbit or human antibody directed against the glycine-alanine repeat sequence. MSWBS contained a truncated as well as a full size **EBNA**-1 polypeptide. It also reacted with antibody directed against the glycine-alanine repeat. This indicates that the repeat sequence is regularly affected by the truncation.

L6 ANSWER 14 OF 27 MEDLINE DUPLICATE 11
AN 95133150 MEDLINE
DN 95133150 PubMed ID: 7831773
TI Characterization of the Epstein-Barr virus Fp promoter.
AU Nonkwelo C; Henson E B; Sample J
CS Department of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105.
NC CA-21765 (NCI)
CA-56639 (NCI)
SO VIROLOGY, (1995 Jan 10) 206 (1) 183-95.
Journal code: 0110674. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199502
ED Entered STN: 19950307
Last Updated on STN: 19950307
Entered Medline: 19950217
AB Expression of the Epstein-Barr virus nuclear antigen-1 (**EBNA**-1) protein is mediated by the virus Fp promoter in Burkitt lymphoma and nasopharyngeal carcinoma. This promoter is silent in latently infected B lymphoblastoid and most Burkitt lymphoma-derived cell lines in vitro, which utilize separate promoters approximately 50 kb upstream of Fp to express **EBNA** proteins. Fp-mediated activation of **EBNA** -1 expression is also activated upon induction of the virus replication cycle. We previously demonstrated that activation of Fp in Burkitt cells requires cis-regulatory elements downstream of the site of transcription initiation. We have now mapped two positive regulatory elements within the Fp promoter. One element contains two potential binding sites for the cellular transcription factor LBP-1 between +138 and +150. A second regulatory element was mapped between +177 and +192 and can be specifically bound in vitro by protein from nuclear extracts of Burkitt cells. Although this element overlaps two partial E2F binding sites and Fp reporter plasmids could be activated in trans by the **adenovirus** E1A protein in cotransfection experiments, mutational analysis and DNA binding studies suggest that these are unlikely to be functional E2F response elements within Fp. We also demonstrate that Fp-directed transcription initiates at multiple sites within both the genome and the Fp reporter plasmids. However, the principal site of transcription initiation within the genome is not utilized within reporter plasmids, in which the majority of transcripts initiate at multiple sites between +150 and +200. This finding suggests that additional elements may be necessary for Fp to function normally in these assays or that the context of Fp within the viral genome is critical to its regulation.

L6 ANSWER 4 OF 27 MEDLINE DUPLICATE 2
AN 2002056565 MEDLINE
DN 21642063 PubMed ID: 11782375
TI Tumor-targeted gene therapy for nasopharyngeal carcinoma.
AU Li Jian-Hua; Chia Marie; Shi Wei; Ngo D; Strathdee Craig A; Huang Dolly; Klamut Henry; Liu Fei-Fei
CS Department of Radiation Oncology, Princess Margaret Hospital/Ontario Cancer Institute, University Health Network, Toronto, Ontario, M5G 2M9 Canada.
SO CANCER RESEARCH, (2002 Jan 1) 62 (1) 171-8.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 20020125
Last Updated on STN: 20020213
Entered Medline: 20020212
AB The unique feature of human nasopharyngeal carcinoma (NPC) is its almost universal association with the EBV, which is expressed in a latent form exclusively in cancer cells, and not in the surrounding tissues. We have exploited this differential by constructing a novel replication-deficient **adenovirus** vector (ad5.oriP) in which transgene expression is under the transcriptional regulation of the family of repeats domain of the origin of replication (oriP) of EBV. When **EBNA1**, one of the latent gene products of EBV, binds to the family of repeats sequence, this activates transcription of downstream genes. Vector constructs were made using the beta-galactosidase and luciferase reporter genes (ad5oriP.betagal and ad5oriP.luc) or the p53 tumor suppressor gene (ad5oriP.p53). 5-Bromo-4-chloro-3-indolyl-beta-D-galactopyranoside staining demonstrated extensive expression only in EBV-positive NPC cells, specifically in response to the presence of **EBNA1**. The relative difference in expression between EBV-positive and -negative cell lines is approximately 1000-fold. This selective expression was corroborated in EBV-positive and -negative tumor models, along with an absence of transgene expression in the host liver. Significant cytotoxicity was achieved using the adv.oriP.p53 therapeutic gene only in EBV-positive NPC cells, which was enhanced with the addition of ionizing radiation. Cytotoxicity was mediated primarily by induction of apoptosis. These results demonstrate that the oriP sequence can achieve high levels of gene expression targeted specifically to EBV-positive NPC cells in the context of the adv vector. This has now provided the tumor-specific expression system from which additional interventions can be evaluated in future treatment strategies for patients with nasopharyngeal cancers.